Frailty in patients with advanced heart failure referred for heart transplantation

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BMedSci (Hons)

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UNIVERSITY OF TECHNOLOGY SYDNEY

Certificate of original authorship

I certify that the work in this thesis has not previously been submitted for a degree nor has it been submitted as part of requirements for a degree except as fully acknowledged within the text. I also certify that the thesis has been written by me. Any help that I have received in my research work and the preparation of the thesis itself has been acknowledged. In addition, I certify that all information sources and literature used are indicated in the thesis.

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(Sunita R. Jha)

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"The 10 years from 18 to 28 comprise the most pivotal decade in a person's life."

- Mintz, S. (2015). *The Prime of Life*. Harvard University Press.

Having spent a good portion of my most pivotal years undertaking this PhD, the mentors, supervisors, colleagues, relationships and friends I've made during this time will have untold influence on my life.

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~ The greatest acknowledgement is to my Mum, Neerja Jha ~

Anthology of publications and presentations

As our research group at St. Vincent's hospital were the first to investigate the impact of frailty in patient's referred for heart transplantation, our work was met with keen interest both nationally and internationally. As frailty is commonly recognised, yet poorly understood within the clinical setting of advanced heart failure, there was a real desire within the transplant community for our team to proactively communicate our findings as they emerged. Accordingly, over the course of this PhD we were fortunate enough to publish the findings in several highly reputable journals and present numerous abstracts across several prestigious conferences. As part of this thesis, there were a total of 4 associated publications and 16 presented abstracts (10 oral: 6 poster), listed below.

Publications associated with this thesis

Sunita R Jha, Malin K Hannu, Phillip J Newton, Kay Wilhelm, Christopher S Hayward, Andrew Jabbour, Eugene Kotlyar, Anne Keogh, Kumud Dhital, Emily Granger, Mark Connellan, Paul Jansz, Phillip M Spratt, Elyn Montgomery, Angela Smith, Michelle Harkess, Peta Tunicliff, Patricia M Davidson, Peter S Macdonald. Reversibility of frailty after bridge-to-transplant ventricular assist device implantation or heart transplantation. *Transplantation Direct*. 2017:3(7). [Impact factor: 3.535; citations: 8]

Sunita R Jha, Malin K Hannu, Keren Gore, Sungwon Chang, Phillip Newton, Kay Wilhelm, Christopher S Hayward, Andrew Jabbour, Eugene Kotlyar, Anne Keogh, Kumud Dhital, Emily Granger, Paul Jansz, Phillip M Spratt, Elyn Montgomery, Michelle Harkess, Peta Tunicliff, Patricia M Davidson, Peter S Macdonald. Cognitive impairment improves the predictive validity of physical frailty for mortality in patients with advanced heart failure referred for heart transplantation. *Journal of Heart and Lung Transplantation.* 2016:35(9):1092-100. [Impact factor: 7.509; citations: 21]

Sunita R Jha, Malin K Hannu, Sungwon Chang, Elyn Montgomery, Michelle Harkess, Kay Wilhelm, Christopher S Hayward, Andrew Jabbour, Phillip M Spratt, Phillip Newton, Patricia M Davidson, Peter S Macdonald. The prevalence and prognostic significance of frailty in patients with advanced heart failure referred for heart transplantation. *Transplantation.* 2016:100(2):429-36. [Impact factor: 3.690; citations: 36]

Sunita R Jha, Hakeem SK Ha, Louise D Hickman, Malin Hannu, Patricia M Davidson, Peter S Macdonald, Phillip J Newton. Frailty in advanced heart failure: A systematic review. *Heart Failure Reviews.* 2015:20(5):553-60 [Impact factor 3.611; citation: 33]

Accepted abstracts for oral presentation as part of this thesis

Jha, S.R. et. al., Reversibility of Fried's Physcial Frailty domains post- heart transplant among patients with advanced heart failure. *Journal of Heart and Lung Transplantation.* International Society of Heart and Lung Transplant (ISHLT), 2018:37(4):S128. Nice, France.

Jha, S.R. et. al., The Impact of Cognitive Frailty on Post-Bridge-to-Transplant Ventricular Assist Device (VAD) Outcomes. *Journal of Heart and Lung Transplantation.* International Society of Heart and Lung Transplant (ISHLT), 2018: 37(4):S128-S129. Nice, France.

Jha, S.R. et. al., Changes in Fried's frailty domains post- ventricular-assist device implantation and heart transplantation. European Society of Cardiology – Heart Failure (ESC-HF), 2017**.** Paris, France.

Jha, S.R. et. al., Reversibility of Frailty Post-VAD Implantation and Heart Transplantation. *Heart, Lung and Circulation,* 2016:25:S120, Cardiac Society of Australia and New Zealand (CSANZ), Adelaide, Australia.

Jha, S.R. et. al., Cognitive Frailty in Heart-Transplant Eligible Patients: A Better Predictor of Mortality. *Heart, Lung and Circulation,* 2016:25:S120, Cardiac Society of Australia and New Zealand (CSANZ), Adelaide, Australia.

Jha, S.R. et. al., Frailty Measures in Advanced Heart Failure Patients Listed for Transplantation. *The Journal of Heart and Lung Transplantation*, 2016:35(4):S27. International Society of Heart and Lung Transplant (ISHLT), 2016. Washington, USA.

Jha, S.R. et. al., Reversibility of Frailty in Advanced Heart Failure Patients Listed for Transplantation. *The Journal of Heart and Lung Transplantation*, 2016:35(4):S27. International Society of Heart and Lung Transplant (ISHLT), 2016. Washington, USA.

Jha, S.R. et. al., The inclusion of cognitive impairment to physical frailty improves survival prediction in heart transplant referred patients. Transplant Society of Australia and New Zealand Annual Scientific Meeting (TSANZ -ASM) – President's Prize Session, 2016. Sydney, Australia.

Jha, S.R. et. al., The reversibility of frailty in heart transplant listed patients. Transplant Society of Australia and New Zealand Annual Scientific Meeting (TSANZ -ASM), 2016. Sydney, Australia.

Hannu, M., **Jha, S.R.** (presenter) et. al., Inclusion of Cognitive and Mood Domains in the Assessment of Frailty Enhances Outcome Prediction in Patients Undergoing Ventricular Assist Device Implantation. Journal of Heart and Lung Transplantation. International Society of Heart and Lung Transplant (ISHLT), 2015. Nice, France.

Accepted abstracts for poster presentation as part of this thesis

Jha, S.R. et. al., Changes in Fried's frailty domains post- ventricular-assist device implantation and heart transplantation. *Journal of Frailty and Ageing*, ICFSR 2017. Barcelona, Spain.

Jha, S.R., et. al., The inclusion of cognitive impairment to physical frailty improves survival prediction in heart transplant referred patients. *Journal of Frailty and Ageing.* 2016:5(1). ICFSR, Philadelphia, USA.

Jha, S.R., et. al., The reversibility of frailty in heart transplant listed patients. *Journal of Frailty and Ageing.* 2016:5(1). ICFSR, Philadelphia, USA.

Jha, S.R. et. al., Does the inclusion of depression and cognitive screening to frailty assessment improve prediction of outcomes in heart transplant-eligible patients?, *European Heart Journal.* 2015(36):500. European Society of Cardiology (ESC) 2015. London, UK.

Jha, S.R., et. al. Frailty as a Predictor of Outcomes in Heart Transplant-Eligible Patients With Advanced Heart Failure. *Journal of Heart and Lung Transplantation*. 4(34):S187-S8 (ISHLT) 2015. Nice, France.

Jha, S.R., et. al. Inclusion of Cognitive and Mood Domains in the Assessment of Frailty Enhances Outcome Prediction in Heart Transplant-Eligible Patients With Advanced Heart Failure. *Journal of Heart and Lung Transplantation*. 4(34):S181 (ISHLT) 2015. Nice, France.

NB:

Abstracts accepted for oral presentation (N=10) are attached as Appendix 4.

Abstracts accepted for poster presentation (N=6) are attached as Appendix 5.

Subsidiary Output

Articles

Rita P, Serenelli M, Bugani G, Tonet E, Celis-Morales C, Gray S, Izawa KP, Colin-Ramirez E, Lilia CM, Izumiya Y, Hanatani S, Onoue Y, Tsujita K, Macdonald PS, **Jha SR,** Roger V, Manemann S, McNallan SM, Sanchis J, Ruiz V, Ferrari R, Volpato S & Campo G. Grip Strength Predicts Cardiac Death and Hospital readmission for Heart Failure in Patients with Cardiac Disease: a Meta-analysis. *JACC: Heart failure 2018.* [under revision].

Mauthner, O., Claes, V., **Jha, S.R.,** Macdonald, P.S. De Geest, S., Handle with care: a scoping review on frailty as a concept and its usefulness in solid organ transplantation. *Transplantation Reviews.* 2017:31(3):218-224.

Mcdonagh, J., Martin, L., Ferguson, C., **Jha, S.R.,** Macdonald, P.S., Davidson, P., & Newton, P.J. Frailty assessment instruments in heart failure: a systematic review. *European Journal of Cardiac Nursing.* 2017:17(1):23-35.

Editorials

Jha, S.R., Mcdonagh, J., Ferguson, C., Macdonald, P.S., & Newton, P.J., Commentary response: Frailty, not just about old people: Reply to Smith GD & Kydd A (2017) Getting care of older people right: the need for appropriate frailty assessment? *Journal of Clinical Nursing*, 2017:26 (23-24). *(Attached as Appendix 10).*

Book Chapter

Newton. P.J., Davidson, P.M., Ivynian, S.E., **Jha, S.R.** Living with Chronic Illness and Disability 3rd edition: Chapter 21 Chronic Heart Failure. eBook ISBN: 9780729542616.

Conference Abstracts

Montgomery, E., Macdonald, P., Newton, P., **Jha, SR** et al., Frailty as a Predictor of Prognostic Outcomes in Patients with Interstitial Lung Disease Referred for Lung Transplantation. *Journal of Heart and Lung Transplantation*. International Society of Heart and Lung Transplant (ISHLT), 2018:37(4):S165. Nice, France.

S, Offen, **Jha, S.R.** et. al., Frailty Predicts Mortality After Heart Transplantation. *Journal of Heart and Lung Transplantation.* International Society of Heart and Lung Transplant (ISHLT), 2018. 37(4):S49. Nice, France.

Montgomery, E., Macdonald, P., Newton, P., Jha, SR et al., Reversibility of Frailty after Lung Transplantation. *Journal of Heart and Lung Transplantation.* International Society of Heart and Lung Transplant (ISHLT), 2018. 37(4):S249. Nice, France.

Jha, S.R. et. al., Twitter as a tool for knowledge translation in #frailty research: A snapshot report. Australian and New Zealand Society for Sarcopenia and Frailty Research (ANZSSFR), 2017. Adelaide, Australia.

McDonagh, J., Prichard, R., Jha, S.R., Furguson, C., Macdonald, P.S., & Newton, P.J. Frailty is highly prevalent among inpatients and outpatients with heart failure according to two frailty measurement instruments. ANZSSFR, 2017. Adelaide, Australia.

Prichard, R., Goodall, S, Macdonald, P.S., J,. Zhao, **Jha, S.R.,** Davidson, P.M., McDonagh, J., Newton, P.J & Hayward, C.S., Frailty is associated with reduced patient reported quality of life in advanced heart failure patients and clinicians are poor at identifying it. ANZSSFR, 2017. Adelaide, Australia.

Wilhelm K, **Jha S.R.** & Macdonald P.S. Adding depression and cognitive function to 'frailty' increases prediction of prognosis in advanced heart failure. WPA XVII World Congress of Psychiatry, Berlin 2017.

Prichard, R., **Jha, S.R.,** McDonagh, J., Zhao, F., Goodall, S., Davidson, P.M., Macdonald, P.S., Hayward, C.S., & & Newton, P.J. Correlating frailty with patient reported quality of life in a cohort of advanced heart failure patients undergoing transplant assessment. *Journal of Frailty and Ageing.* ICFSR, 2017.

McDonagh, J., Martin, L., Furguson, C., **Jha, S.R.,** Macdonald, P.S., Davidson, P.M., & Newton, P.J. How is frailty measured in individuals with heart failure? A systematic review. Journal of Frailty and Ageing. *Journal of Frailty and Ageing.* ICFSR, 2017.

Montgomery, E., Macdonald, P.S.,… **Jha, S.R.** (last author). The Prevalence and Prognostic Significance of Frailty in Patients with Advanced Lung Disease Referred for Lung Transplantation. *The Journal of Heart and Lung Transplantation*. Vol. 35, Issue 4, S29, 2016. ISHLT, 2016.

McDonagh, J., Ferguson, C., **Jha, S.R.,** et. al., Frailty in hospitalized heart failure patients predicts death and rehospitalisation at 6 month. *Journal of Frailty and Ageing.* ICFSR, 2016:5(1).

Ivynian S, DiGiacomo M, **Jha, S.R.,** Crossley C, Newton P. Care-seeking decisions for worsening symptoms in Heart Failure: a qualitative metasynthesis. *Heart, Lung and Circulation.* CSANZ. 2015:24(6):S419, 2015.

Awards granted as part of this thesis

UTS Doctoral Scholarship – University of Technology Sydney

Transplant Society of Australia and New Zealand (TSANZ): Travel Grant

Transplant Society of Australia and New Zealand (TSANZ): Young Investigator Award: Top Clinical Presentation - Runner up

Cardiac Society of Australia and New Zealand (CSANZ) Heart Failure Council Travel Grant

Health Services and Practice Research Student Development Award (HSP)

UTS Research Student Forum: Best Oral Presentation

Vice-Chancellor's Postgraduate Research Student Conference Grant

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Abbreviations

AHF	advanced heart failure
BMI	body mass index
CAD	coronary artery disease
CI	cardiac index
DMI-10	Depression in Medical Illness-10
FP	Fried Phenotype
GFR	glomerular filtration rate
HTx	heart transplantation
LOS	length of stay
LVAD	left ventricular assist device
LVEF	left ventricular ejection fraction
MCS	mechanical circulatory support
MoCA	Montreal Cognitive Assessment
MPAP	mean pulmonary artery pressure
NYHA	New York Heart Association
PAWP	pulmonary artery wedge pressure
RAP	right arterial pressures
Se	serum
SHARE-FI	Survey of Health, Ageing and Retirement in Europe – Frailty Index
VAD	ventricular assist device

Abstract

Intro

Frailty research within advanced heart failure (AHF) is a nascent concept. Frailty is defined as an increased vulnerability to stressors in response to an individual's declining physiological reserve. As physiological reserves naturally decline with advancing age, frailty is considered a geriatric syndrome. While the significance of frailty is well entrenched within geriatric medicine, the impact of frailty among other specialties is only emerging. The increased survival of an ageing highly co-morbid populace of heart failure patients alongside the expanding use of invasive surgical interventions, has propelled frailty exploration into the forefront of cardiovascular research. This thesis by publication represents the first set of studies to explore the impact of frailty in patients with advanced heart failure referred for heart transplantation.

Aim

As the age of patients being referred, listed and transplanted has steadily risen over the last two decades, the overall aim of this thesis was to objectively identify these older high-risk patients. Four distinct and interrelated publications make up this thesis, each with a different objective:

Study 1: A systematic review to identify the contemporary understanding of frailty in patients with AHF.

Study 2: To identify the impact of physical frailty among patients with AHF referred for heart transplantation.

Study 3: To identify if the addition of cognitive impairment, depression or both to the physical measure of frailty improves its predictive capacity.

Study 4: To identify if frailty pre-intervention reverses post-intervention.

Method

Study 1 - Systematic Review: A review of the key databases was conducted from 2004 – 2014 including the key search terms 'frail elderly' and 'heart failure'. The following electronic databases were searched: Medline, Cumulative Index for Nursing and Allied Health (CINAHL) and Academic search complete, with reference lists being manually searched. Articles were included if frailty was assessed using a valid measuring tool in a population with a confirmed diagnosis of advanced heart failure.

Study 2, 3 & 4 - Observational cohort study. In 2013 all patients referred for heart transplantation were assessed for frailty, cognitive impairment and depression. Frailty was assessed using Fried's Frailty Phenotype (FP). As part of this measure five functional domains were measured: Weakness, physical inactivity, exhaustion, slowness and reduced appetite. If three or more domains are present from the five, a patient was identified as frail and less than three denotes no frailty. Cognitive impairment was assessed using the Montreal Cognitive Assessment (MoCA). A MoCA score of 26 or less was indicative of cognitive impairment. The Depression in Medical Illnesses (DMI-10) tool was used to identify depression. A DMI score greater

than 9 is indicative of depression. Patient demographics and markers of disease severity were obtained. Among those undergoing either bridge to transplant ventricular assist device implantation (BTT-VAD) or heart transplantation (HTx), post-interventional outcomes (intubation time, ICU stay and hospital length of stay) were examined. Overall survival and post-interventional survival were explored. For those identified as frail pre-intervention, frailty was re-assessed at least 2 months post-intervention for syndrome reversal.

Results

Study 1 - Systematic Review: The search yielded a total of 393 articles with 8 articles being selected for review. The prevalence of frailty among those with AHF was high, ranging from 18-54%. The Frailty Phenotype and Geriatric assessments tools were the most common frailty measures utilised; high rates of co-morbidity, hospitalisation and mortality were identified.

Observational cohort studies:

Study 2 - 120 patients (83M; age 53±12 years, range 16-73; LVEF 27±14%) underwent frailty assessment. 39/120 (33%) were assessed as frail. Frailty was associated with NYHA Class IV heart failure, lower body mass index, elevated intra-cardiac filling pressures, lower cardiac index, anaemia, hypoalbuminemia, hyperbilirubinemia, cognitive impairment and depression (all $\rho < 0.05$). Frailty status was independent of age, gender, heart failure duration, left ventricular ejection fraction or renal function. Frailty was an independent predictor of increased all-cause mortality: one year actuarial survival was 79±5% in the non-frail group compared with only 54±9% for the frail group ($p < 0.005$).

Study 3 - 156 patients (109M; age 53±13 years; LVEF 27±14%) underwent assessment of frailty. Inclusion of cognitive impairment or depression or both to the definition of physical frailty (i.e. PF+MoCA, or PF+DMI or PF+MoCA+DMI; Frail ≥ 3) increased the proportion classified as frail: from 33% using PF to 42% with "cognitive frailty" (PF+MoCA). Twenty eight patients died during follow-up prior to ventricular assist device (VAD) implantation or HTx. Frailty was associated with significantly lower VAD- and HTx-free survival, with cognitive frailty best capturing early mortality: 12 month survival for non-frail and frail cohorts was 81 $\pm$ 5% vs 58 $\pm$ 10% ($p < 0.02$) using PF and 85 $\pm$ 5% vs 56 $\pm$ 9% ($p < 0.002$) using cognitive frailty. Combining DMI with PF or cognitive frailty did not strengthen the relationship between frailty and mortality.

Study 4 - 100 patients underwent frailty assessment prior to surgical intervention: 40 (21 non-frail, 19 frail) BTT-VAD and 77 (60 non-frail, 17 frail) HTx - including 17 of the 40 BTT-VAD supported patients. Frail patients had lower survival (63±10% versus 94±3% at one year, p=0.012) and experienced significantly longer ICU (11 versus 5 days, p=0.002) and hospital (49 versus 25 days, p=0.003) length of stay after surgical intervention compared with non-frail patients. Twelve of 13 frail patients improved their frailty score after VAD (4.0±0.8 to 1.4 ± 1.1, $p < 0.001$) and 12/13 frail patients improved their frailty score after HTx (3.2±0.4 to 0.9±0.9, $p < 0.001$). Hand-grip strength and depression improved post-intervention. Only a slight improvement in cognitive function was seen post-intervention.

Conclusion

The initial hypothesis was that frailty in this population would provide an ideal measure of vulnerability among *older* transplant referred patients. While this hypothesis was rejected, frailty was found to be an *age-indiscriminate measure of patient vulnerability*. The studies presented as part of this thesis demonstrate that frailty is highly prevalent among people referred for heart transplantation, being frail pre-interventions independently increases the risk of early mortality but in those patients that survive the early periods post intervention, frailty can reverse.

Recommendations from this thesis

At the conclusion of this thesis, there were 3 main suggested recommendations for future research to improve clinical practice in this space.

Recommendation 1

It is recommended that frailty not be subjectively identified by visual appearance (i.e. "eye-ball-test"/"end-of-the-bed-test"), and that validated HF-specific frailty screening tools should be incorporated as part of the standard care for all referred patients undergoing heart transplant

Recommendation 2

Further research is needed to enable us to differentiate between VAD-responsive frailty and VAD-independent frailty. Once able to determine which listed frail patients are likely to be responsive to VAD-implantation, making the clinical decision to prioritise VAD-implantation should be recommended. The investigation of metabolomics profiling in this area may provide the key answers, and warrants piloting research.

Recommendation 3

The impact of frailty pre-habilitation among those with advanced heart failure needs to be evaluated. It is probable that an exercise-based intervention would be effective in reducing non-cardiac induced frailty among referred patients. This however represents a gap in the evidence and is a high-priority area for further research.